EFFICACY REVIEW

PRODUCT: SVP7 (marketed name = Vectra 3D)

DATE: July 26, 2012

FILE SYMBOL: 83399-6

DP BARCODE: 401936

DECISION: 463205

GLP: Varied

CHEMICALS: Permethrin (36.08%) + Pyriproxyfen (.44%) + Dinotefuran (4.95%)

CHEMICAL NUMBERS: Permethrin - 109701   Pyriproxyfen – 129032   Dinotefuran - 044312

PURPOSE: To add marketing claims on all life stages of fleas, bed bugs & prevention of attachment

MRIDs:

New Data:

MRID 48787101: Comparative efficacy in vivo of a dermal treatment based on dintefuran vs. Frontline Plus & K9 Advantix against the adult and immature cat flea (*Ctenocephalides felis*) and the adult brown dog tick (*Rhipicephalus sanguineus*) with repeated dosing over 4 months in dogs housed outdoors

MRID 48787103. Prevention of Feeding of Vectra 3D for Dogs and Puppies Spot-On Treatment Against the Cat Flea (Ctenocephalides felis) on dogs
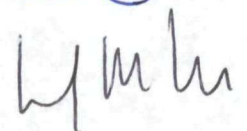
Cited Data:

MRID 47573001. Donahue, W. (2008) In vitro Efficacy Evaluations of Permanone 40 MFG Concentrate Against Selected Arthropod Pest Species: Final Report. Project NumberVBS05/3C. Unpublished study prepared by Sierra Research Labs. 204 p.

TEAM REVIEWER: Rita Kumar

EFFICACY REVIEWER: Autumn Metzger, M.S.   7/26/12

**SECONDARY EFFICACY
REVIEWER:**   Jennifer Urbanski, Ph.D.   7/26/12

1

BACKGROUND

SVP7 is a topical spot-on insecticide treatment for the control of fleas and ticks for dogs and puppies 7 weeks of age and older. The product is applied on the skin between the shoulder blades once monthly.

Labeled Application Rates:

Dog Size	Application Rate
Dogs & Puppies older than 7 weeks 2.5-20 lbs	1.6 ml
Dogs 21-55 lbs	3.6 ml
Dogs 56-95 lbs	4.7 ml
Dogs >95 lbs	8.0 ml

DATA REVIEW

The following data review is comprised of explanations of materials and methods, and a summation of experimental results containing tables with reformatted data.

MRID 48787101: Comparative efficacy in vivo of a dermal treatment based on dintefuran vs. Frontline Plus & K9 Advantix against the adult and immature cat flea (*Ctenocephalides felis*) and the adult brown dog tick (*Rhipicephalus sanguineus*) with repeated dosing over 4 months in dogs housed outdoors.

Objective
To evaluate the effectiveness of an experimental formulation of Vectra 3D (a dinotefuran compound) vs. 2 positive controls against the cat flea and the brown dog tick on dogs outdoors.

GLP: No

Set Up
Thirty-two dogs, weighing 21-55 lbs, 1-9 years old were split into 4 groups of 8 dogs. Dogs were housed outdoors but allowed shelter at their pleasure and during & after tick/flea challenges for 2-5 days at a time.
Group 1 = placebo/negative control
Group 2 = treated with "an experimental formulation" named TTE, and discussed as Vectra 3D (Dinotefuran + Pyriproxyfen + Permethrin – all at the % a.i. of the marketed product)
Group 3 = Frontline Plus (Fipronil + S-Methoprene)
Group 4 = K9 Advantix 55 (Permethrin + Imidacloprid)

Dogs were treated on days 0, 30, 60 & 90. They were infested with 50 ticks on days 28, 44, 88, & 104 and tick were counted and removed 48 hours later.
They were infested with 100 cat fleas on days 14, 55, 74, 115 & 150. Fleas were counted and removed 24 hours later, except on the last day they were collected on day 154 to allow for egg collection.

Ovicidal assessment were performed by collecting ~50 flea ova from dogs (if possible) on days 18, 59, 78, 119 & 154 or the day after if more were needed to reach 50. Ova were place in media for 32 days for incubation and pupae that were harvested were allowed to emerge into adults and counted ~ 28 days later.

Results

Fleas - On all counts, fleas were decreased versus the control by >90 % (see table 1).
Ticks - On all counts, ticks were decreased versus the control by >90 % (see table 2).
Flea eggs – Nearly zero eggs hatched giving 98.7-100% efficacy vs. control for eggs collected at each count (see table 3).

Table 1. Adult Flea counts

Table 4A. Summary of geometric mean flea (*Ctenocephalides felis*) counts (and percent efficacy) for dogs treated topically with Vectra vehicle, Vectra 3D™, Frontline Plus® or K9 Advantix® 55 on Days +0, +30, +60 and +90

Day[1]	Control	Vectra 3D™		Frontline Plus®		K9 Advantix® 55	
-11	67.4	67.5		68.4		69.0	
+15 (15)	76.3	1.1^B	(98.6%)	0.3^B	(99.7%)	1.1^B	(98.6%)
+56 (26)	74.5	1.3^B	(98.3%)	0.7^B	(99.1%)	1.6^B	(97.9%)
+75 (15)	81.6	0.1^B	(99.9%)	0.0^B	(100%)	0.0^B	(100%)
+116 (26)	76.2	0.2^B	(99.8%)	0.5^B	(99.4%)	0.9^B	(98.9%)
+154 (64)	76.4	6.3^B	(91.7%)	1.2^B	(98.4%)	8.4^B	(89.1%)

[1] Day of study (number of days since most recent treatment)
^{B} Significantly different from control (p<0.01)
There was no significant difference between Vectra 3D™ and either Frontline Plus® or K9 Advantix® 55 at any assessment (p>0.05)

Table 2. Tick Counts

Table 5A. Summary of geometric mean tick (*Rhipicephalus sanguineus*) counts (and percent efficacy) for dogs treated topically with Vectra vehicle, Vectra 3D™, Frontline Plus® or K9 Advantix® 55 on Days 0, +30, +60 and +90

Day[1]	Control	Vectra 3D™		Frontline Plus®		K9 Advantix® 55	
-3	20.1	21.9		19.5		21.9	
+30 (30)	21.8	1.5^B	(93.2%)	13.5^{B,D}	(38.0%)	4.1^B	(81.4%)
+46 (16)	22.5	0.4^B	(98.4%)	0.1^B	(99.6%)	0.3^B	(98.9%)
+90 (30)	20.1	0.9^B	(95.3%)	10.5^{B,D}	(47.7%)	0.3^B	(98.6%)
+106 (16)	23.2	1.7^B	(92.6%)	3.3^B	(85.8%)	0.6^B	(97.4%)

[1] Day of study (number of days since most recent treatment)
^{B} Significantly different from control (p<0.01)
^{D} Significantly different from Vectra 3D™ (p<0.01)

Table 3. Cat flea emergence

Table 6A. Summary of retransformed[1] mean flea egg percentage hatch and percentage adult emergence (and percent efficacy) for dogs treated topically with Vectra 3D™, Frontline Plus®, K9 Advantix® 55 or Vectra vehicle on Days 0, +30, +60 and +90, for eggs collected at the indicated days

Day[2]	Control	Vectra 3D™		Frontline Plus®		K9 Advantix® 55	
Percent hatch							
+18-+19 (18-19)	78.1	0.0^B	(100%)	0.0^B	(100%)	0.0^B	(100%)
+59-+60 (29-30)	74.6	0.0^B	(100%)	0.0^B	(100%)	0.0^B	(100%)
+78-+79 (18-19)	75.1	0.0^B	(100%)	0.0^B	(100%)	0.0^B	(100%)
+119-+120 (29-30)	80.7	0.0^B	(100%)	0.0^B	(100%)	0.0^B	(100%)
+153-+154 (63-64)	79.6	1.0^B	(98.7%)	0.2^B	(99.7%)	$33.7^{B,D}$	(57.7%)
Adult emergence							
+18-+19 (18-19)	74.3	0.0^B	(100%)	0.0^B	(100%)	0.0^B	(100%)
+59-+60 (29-30)	73.9	0.0^B	(100%)	0.0^B	(100%)	0.0^B	(100%)
+78-+79 (18-19)	74.8	0.0^B	(100%)	0.0^B	(100%)	0.0^B	(100%)
+119-+120 (29-30)	80.4	0.0^B	(100%)	0.0^B	(100%)	0.0^B	(100%)
+153-+154 (63-64)	78.3	1.0^B	(98.7%)	0.1^B	(99.9%)	$26.5^{B,D}$	(66.2%)

[1]Based on transformation to the arcsine of the square root of the proportion
[2]Days of egg collection (number of days since most recent treatment)
[B]Significantly different from control ($p<0.01$)
[D]Significantly different from Vectra 3D™ ($p<0.01$)

Conclusion

This data can be used as supplementary to continue to support the claims that Vectra 3D is efficacious against adult cat fleas, adult brown dog ticks and flea eggs and that it works on dogs that go outdoors. This study could not be used on its own to support any claims as it does not challenge for 14 days after treatment for fleas and 28 days for ticks. It also did not contain information on amount of sunlight or rain each dog was exposed to; therefore no further sunlight or rain claims can be given. **This data does not support any new claim.**

4

MRID: 48787103. Prevention of Feeding of Vectra 3D for Dogs and Puppies Spot-On Treatment Against the Cat Flea (*Ctenocephalides felis*) on dogs

GLP: Yes

Objective
To evaluate the prevention of feeding of cat fleas on dogs treated once a month with Vectra 3D vs. untreated control.

Set Up
Sixteen beagle dogs aged > 6 months were split into 2 groups of 8 dogs. Groups 1 was a non-treated control and group 2 was treated with Vectra 3D at the labeled rate. Dogs were treated on days 0, 28 & 56 and infested with 150 cat fleas on days 8, 12, 16, 20, 36, 40, 43, 48, 69, 72 &76. Dogs were housed in indoor/outdoor runs. Fleas were counted anywhere from 5-60 min after infestation by dogs being combed for 3 minutes with a fine-tooth flea comb. Fortyfive fleas were collected from each combing, however if 45 fleas could not be recovered, the remainder of fleas were collected from boards in the bottom of the cage of each dog. After each count, each dog was given an oral tablet that kills fleas (Capstar, active ingredient Nitenpyram) to "allow for re-use of dogs for multiple time points." See table 1 for study design.

Capstar is an FDA approved insecticide product that kills adult fleas on dogs and cats. The product label states that it begins to work in 30 min with 90% efficacy in 4 hours on dogs. For typical infestations it works for 1 week but for severe infestations 2 tablets per week can be given until the adult fleas are no longer observed.

Table 1. Study Design

Study day*	Weigh dogs	Physical examinations	Infestations**	Nitenpyram (all dogs)	Excipients (control; 8 dogs)	Vectra 3D (8 dogs)	Flea Enumeration/Removal (minutes after infestation)
-12	✔						
-6							
-3		✔****	✔				Remove any remaining fleas******
-2	✔						Comb to enumerate fleas; allocate to TX groups
-1							Remove any remaining fleas******
0					✔	✔	
4				✔****			
7							Remove any remaining fleas******
8		✔	✔	✔****			(5 minutes)*****minimum of 45 fleas
11							Remove any remaining fleas******
12			✔	✔****			(15 minutes) minimum of 45 fleas
14							Remove any remaining fleas******
16			✔	✔****			(25 minutes) minimum of 45 fleas
19							Remove any remaining fleas******
20			✔	✔****			(45 minutes) minimum of 45 fleas
26							Remove any remaining fleas
28	✔				✔	✔	
36			✔	✔****			(10 minutes) minimum of 45 fleas
39							Remove any remaining fleas******
40			✔	✔****			(20 minutes) minimum of 45 fleas
42							Remove any remaining fleas******
43			✔	✔****			(30 minutes) minimum of 45 fleas
47							Remove any remaining fleas******
48			✔	✔****			(60 minutes) minimum of 45 fleas
51							Remove any remaining fleas******
56	✔				✔	✔	
69			✔	✔****			(15 minutes) *****minimum of 45 fleas
71							Remove any remaining fleas******
72			✔	✔****			(25 minutes) *****minimum of 45 fleas
75							Remove any remaining fleas******
76			✔	✔****			(60 minutes) *****minimum of 45 fleas

*All dogs will observed hourly after treatment with Vectra 3D or excipients on days 0, 28 sand 56. All dogs will be observed twice daily on all remaining study days.
**Each dog will be infested with 150 unfed adults fleas ([100 on day -3]; approximately 50% male; 50% female). ***Perform physical examination between days -12 and -3.
****Nitenpyram will be administered immediately after collections on days 8, 12, 16, 20, 36, 40, 43, 48, 69, 72, and 76. *****Dogs will combed for 3 minutes after each start period (I.e. 5-8 min, 15-18 min, 25-28 min, etc.). ******Performed to avoid flea carry-over.

6

Collected fleas were placed in containers and frozen. Aliquots of ten fleas each were microcentrifuged and quantitative real time analysis (qPCR) was conducted. qPCR allows for the dection of blood in fleas to determine if they have fed, and only requires a few fleas to conduct the assay. The presence of a gene code for an enzyme necessary for heme formation can be qualified as a unit of measurement for blood volume consumed by the fleas.

Results

Table 2. Geometric mean copies of HMBS amplicons/10 fleas.

Time on the dog (min)	Treatment with excipients	SEM		Treatment with Vectra 3D	SEM	
		-	+		-	+
5	5.07[a]	3.28	7.85	1.29[b]	0.84	2.00
10	6.93[a]	4.91	9.79	1.0[b]	0.71	1.41
15	6.29[a]	3.56	11.13	3.03[a]	1.71	5.35
20	166.46[a]	108.96	254.32	7.74[b]	5.06	11.82
30	215.08[a]	134.22	344.67	23.36[b]	14.58	37.43
45	114.00[a]	78.27	166.04	31.70[b]	21.77	46.17
60	147.27[a]	111.64	194.28	28.82[b]	21.85	38.02

*SEM=Standard Error of the Mean
[a,b]=Mean with different superscripts are significantly different ($p \leq 0.05$)

Table 3. % efficacy of unfed fleas in treated group vs. control based on geometric means

time on dog (min)	mean of treated group	% efficacy
5	1.29	74.5
10	1	85.5
15	3.03	51.8
20	7.74	**95**
30	23.36	**89**
45	31.7	72
60	28.82	80

Results were analyzed and provided only by time period (minutes collected) after infestation vs. by day. Given this information, 90% efficacy of unfed fleas was only achieved at 20 minutes post-infestation and reached 89% at 30 minutes.

Conclusion

Given that the dogs were treated with an additional insecticide after each infestation, sometimes only 4 days apart, **the study is considered invalid.**

In addition, efficacy was only achieved at 1 time point and reached 89% at another. Even if they had not been given an additional insectidal treatment, it is difficult to determine from the type of analysis performed (qPCR) and the way the time points were analyzed (minutes versus by days) whether the results would have been meaningful. It is also noted that the first time point of infestation was 8 days post-treatment. It would be necessary to test the animals within the first 24-48 hours of the first treatment.

The study does not support any claims.

MRID 47573001. Donahue, W. (2008) In vitro Efficacy Evaluations of Permanone 40 MFG Concentrate Against Selected Arthropod Pest Species: Final Report. Project NumberVBS05/3C. Unpublished study prepared by Sierra Research Labs. 204 p.

The cited data was submitted to support claims of efficacy against bed bugs on dogs and was previously reviewed by M. Suarez on 3/3/2009 (DP 359380).

The study was conducted on numerous species of insects using direct spray of varying dilutions of a permethrin manufacturing use product.

The study, the rates and the product used do not translate to a pet spot on product and cannot be used to support any claims. In addition, it is not appropriate to have bed bug claims on a pet spot on product.

RECOMMENDATIONS:

<u>**Delete the following proposed claims:**</u>

All claims and references to bed bugs
Pg 6: starts to kill fleas within minutes
Pg 8:
- repels and kills ticks before they can attach to dogs (and take a blood meal)
- kills ticks quickly, before they take a blood meal
- quickly kills ticks on contact
- kills ticks quickly

Pg 12:
- Protects dogs when they travel
- Protects traveling dogs
- SVP7 together with heartworm preventative may be helpful in providing an extra layer of protection against possible transmission from feeding mosquitoes that may be carrying heartworm larvae – as noted in efficacy review dated 10/4/2010.

- Effectively targets all flea life stages (data only showed decreased emergence of flea eggs and did not prove it was effective against pupae).

Page 13:
- Starts killing fleas in 5 minutes (only "Begins reducing flea feeding in 5 minutes" was previously accepted but not killing in 5 minutes)
- Fast acting starts killing fleas in (as little as) 5 minutes
- Starts rapidly killing species of ticks…
- Prevents fleas on treated dogs from infesting your home
- Kills through contact so pets don't have to bite to die

All other added claims are acceptable based on claims already approved on the last accepted label, however no new claims are supported with this submission.